

REMARKS

Claim Status

Claims 38 and 39 have been amended to recite that the one or more point mutations result in at least one amino acid substitution of Asp165 to Gly and that the modified polypeptide further comprises one or more of the amino acid substitutions selected from the group consisting of His231 replaced by arginine, Ser311 replaced by alanine, leucine or threonine, Asn313 replaced by threonine, Glu317 replaced by lysine, and Gln348 replaced by arginine. Claim 46 has been amended similarly. Support for these amendments is found at least in Table 2, pages 16-20 of the instant specification. Detailed analysis of the support in Table 2 is presented in the following 35 U.S.C. §112 rejection section.

Claim 40 has been amended to recite that the modified polypeptide comprises one or more amino acids within loop $\beta 1, \alpha 8$ replaced with one or more amino acids having increased hydrophobicity, wherein said one or more amino acid replacement is selected from the group consisting of Ser311 replaced by alanine, isoleucine, leucine, or threonine, Asn313 replaced by arginine, histidine, threonine or valine, and Glu317 replaced by alanine, asparagine, lysine or valine. Support for this amendment is found at page 31, lines 8-12 and Table 2 of the instant specification.

New claims 47-49 have been added. Support for these new claims is found in Table 2 of the instant specification.

Claim 41 has been amended to include desired dependency in view of the new claims 47-49.

Pursuant to 37 C.F.R. §1.118(a), Applicants respectfully submit that the above amendments do not introduce any new material into the application. With the present amendments, there are 12 claims pending, namely, claims 38-49.

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Rejection under 35 U.S.C. § 112, first paragraph

Claims 38-46 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner indicated that the phrase “one or more point mutations ... Lys189 to Gly” in claims 38-39 and 44 or the phrase “further comprises the amino acid substitutions ... Gln348 to Arg” in claims 38-40 were not supported in the instant specification or the originally filed claims. In response, Applicants submit the following remarks.

Applicants first request for entry and consideration of the amendments made to Table 2 that were previously submitted in Supplemental Response to Office Action dated March 01, 2005. Applicants note that there is no acknowledgment in this final Office Action that the Examiner has entered and/or considered those amendments as the Examiner suggests that there is no support for “Arg162 to His” in Table 2. For the Examiner’s convenience, Applicants herewith enclose a copy of Table 2 as amended previously (Exhibit A).

Regarding claims 44-45, the Examiner rejects the use of the phrase “one or more point mutations ... Lys189 to Gly” for allegedly lacking support. Applicants submit that the instant specification describes modifications of wild-type Cry3Bb nucleotides at one or more sites, which result in a change in one or more amino acid residues in the modified crystal proteins. The instant specification further describes that the one or more sites could be in helices regions. The following table presents the citation from the related sections of the instant specification, which provides the written support for the rejected phrase.

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Table of Support

Places in the Specification	Citation
Page 15, lines 3-8	... at least one, and preferably, more than one, and most preferably, a significant number, of wild-type <i>cry3</i> nucleotides have been replaced with one or more nucleotides, or where one or more nucleotides have been added to or deleted ...
Page 22, line 6; line 19; lines 22-25; lines 28-29;	...modified crystal proteins having one or more alterations introduced... ... the mutagenesis of one or more codons within the sequence of a toxin mutations may also be made in insecticidal crystal proteins, including ...helices regions Cry3Bb* variants ... that have one or more changes incorporated into the amino acid sequence of the protein ...
Page 23, lines 11-13; Lines 15-18;	... mutations in the amino acid sequences or underlying DNA gene sequences which result in the insertion or deletion of one or more amino acids mutate or delete one or more nucleotides from the nucleic acid sequences of the genes encoding such polypeptides, or alternatively ... add one or more nucleotides into the primary nucleic acid sequence at one or more sites in the sequence ...
Page 29, lines 13-15	... introducing one or more mutations into the nucleic acid sequence to produce a change in one or more amino acid residues in the encoded polypeptide sequence ...
Page 41, lines 8-9	... the <i>cry3</i> * gene encodes an amino acid sequence in which one or more amino acid residues have been changed ...

Clearly, there is support from the instant specification for the phrase “one or more point mutations result in at least one amino acid substitution”. Further with respect to the phrase “selected from the group consisting of Leu158 to Arg, Ser160 to Asn, Lys161 to Pro, Arg162 to His, Asp165 to Gly, Lys189 to Gly”, Applicants submit that the above 6 point mutations are all in or near α helix 4 region, which is one of the helices regions, and that specific examples are

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provided in Table 2 of the instant specification, which have at least one amino acid substitution selected from the group consisting of Leu158 to Arg, Ser160 to Asn, Lys161 to Pro, Arg162 to His, Asp165 to Gly, Lys189 to Gly. Those examples include variants 11221, 11032, 11035, 11046, 11051, 11057, 11058, 11081, 11082, 11084 and 11098.

Regarding claims 38-39 and 46, the Examiner rejects the use of the phrases “one or more point mutations ... Lys189 to Gly” and “further comprises the amino acid substitutions ... Gln348 to Arg” for allegedly lacking support. Applicants present the following remarks.

First, Applicants note that claims 38 and 39 have been amended to recite that the one or more point mutations result in at least one amino acid substitution of Asp165 to Gly and that the modified polypeptide further comprises one or more of the amino acid substitutions selected from the group consisting of His231 replaced by arginine, Ser311 replaced by alanine, leucine or threonine, Asn313 replaced by threonine, Glu317 replaced by lysine, and Gln348 replaced by arginine. Claim 46 has been amended similarly. Applicants submit that support for the combination of Asp165 to Gly and at least one of the claimed amino acid substitutions at positions of 311, 313 and 317 is evident from the general description in the instant specification of “regions may be identified in one or more domains of a crystal protein” for introduction of “one or more alterations” (emphasis added) (*see* page 22, lines 6-11), “identifying from the plurality of mutated polypeptides one or more regions of the Cry3Bb δ -endotoxin for targeted mutagenesis” (emphasis added) (*see* page 31, lines 22-23), and “a crystal protein having one or more mutations in one or more regions of the peptide” (emphasis added) (*see* page 41, lines 6-7), as well as specific examples provided in Table 2 of the instant specification. Those examples include variants 11081, 11082, 11084 and 11098.

Regarding claims 40-43, the Examiner rejects the use of the phrase “further comprises the amino acid substitutions ... Gln348 to Arg” for allegedly lacking support. Applicants present the following remarks.

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First, Applicants note that claim 40 has been amended to recite that the modified polypeptide comprises one or more amino acids within loop $\beta 1, \alpha 8$ replaced with one or more amino acids having increased hydrophobicity, wherein said one or more amino acid replacement is selected from the group consisting of Ser311 replaced by alanine, isoleucine, leucine, or threonine, Asn313 replaced by arginine, histidine, threonine or valine, and Glu317 replaced by alanine, asparagine, lysine or valine.

Support for the phrase “one or more amino acids within loop $\beta 1, \alpha 8$ replaced with one or more amino acids having increased hydrophobicity” is found at page 31, lines 8-12 of the instant specification, wherein nearly identical phrase “replacing one or more amino acids within loop $\beta 1, \alpha 8$, with one or more amino acids having increased hydrophobicity” is used.

Support for the amendment of “wherein said one or more amino acid replacement is selected from the group consisting of Ser311 replaced by alanine, isoleucine, leucine, or threonine, Asn313 replaced by arginine, histidine, threonine or valine, and Glu317 replaced by alanine, asparagine, lysine or valine” is found in Table 2 of the instant specification, wherein specific examples of variants 11228, 11229, 11230, 11231, 11232, 11233, 11235, 11236, 11237, 11238, 11239, 11081, 11082, 11084 and 11098 are provided. New claims 47-49 also find support in Table 2 of the instant specification, wherein specific examples of variants 11231, 11235, 11082, 11084, 11098 and 11228 are provided.

For the Examiner’s convenience, Applicants present the following table summarizing specific variants that are encompassed by claims 44-45; claims 38-39 and 46; and claims 40-43 and 47-49, respectively. Applicants note that the below table is adapted from Table 2 of the instant specification.

Related Variant Table

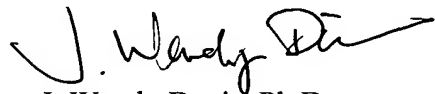
Variant	Amino Acid Changes	Structural Site of Changes	Claims Supported
11221	T154F, P155H, L156H, L158R	$\text{l}\alpha 3,4$	44-45
11032	D165G	$\alpha 4$	44-45
11035	S160N, K161P, R162H, D165G	$\alpha 4$	44-45
11046	S160N, K161P, R162H, D165G, I289V, S293P	$\alpha 4$; $\text{l}\alpha 7, \beta 1$	44-45
11051	K189G	$\text{l}\alpha 4,5$	44-45
11057	D103E, Δ A104, S160N, K161P, R162H, D165G	$\text{l}\alpha 2a,2b$; $\alpha 4$	44-45
11058	D103E, Δ A104, T154F, P155H, L156H, L158R	$\text{l}\alpha 2a,2b$; $\text{l}\alpha 3,4$	44-45
11081	D165G, S311T, E317K	$\alpha 4$; $\text{l}\beta 1, \alpha 8$	38-39 and 46; 44-45; 40-43
11082	D165G, I289V, S293P, F305S, S311A, L312V, Q316W, Q348R, V365A	$\alpha 4$; $\text{l}\alpha 7, \beta 1$; $\beta 1$; $\text{l}\beta 1, \alpha 8$; $\beta 2$; $\beta 3b$	38-39 and 46; 44-45; 40-43 and 49
11084	D165G, S311L	$\alpha 4$; $\text{l}\beta 1, \alpha 8$	38-39 and 46; 44-45; 40-43 and 47
11098	D165G, H231R, S311L, N313T, E317K	$\alpha 4$; $\alpha 6$, $\text{l}\beta 1$, $\alpha 8$	38-39 and 46; 44-45; 40-43 and 47-48
11228	S311L, N313T, E317K	$\text{l}\beta 1, \alpha 8$	40-43 and 47
11229	S311T, E317K, Y318C	$\text{l}\beta 1, \alpha 8$	40-43
11230	S311A, L312V, Q316W	$\text{l}\beta 1, \alpha 8$	40-43
11231	H231R, S311L, N313T, E317K	$\alpha 6$; $\text{l}\beta 1, \alpha 8$	40-43 and 47-48
11232	S311T, L312P, N313T, E317N	$\text{l}\beta 1, \alpha 8$	40-43
11233	S311A, Q316D	$\text{l}\beta 1, \alpha 8$	40-43
11235	H231R, S311L	$\alpha 6$; $\text{l}\beta 1, \alpha 8$	40-43; 47-48
11236	S311I	$\text{l}\beta 1, \alpha 8$	40-43
11237	S311I, N313H	$\text{l}\beta 1, \alpha 8$	40-43
11238	N313V, T314N, Q316M, E317V	$\text{l}\beta 1, \alpha 8$	40-43
11239	N313R, L315P, Q316L, E317A	$\text{l}\beta 1, \alpha 8$	40-43

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In view of the above remarks, it is believed that the subject matters of Claims 38-46 are indeed described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Therefore, Applicants respectfully request that the present rejection be removed.

This response is filed timely and no fee is believed to be due; however, should any fees be required for any reason relating to this document, the Commissioner is authorized to deduct the fees from Howrey LLP Deposit Account No. 01-2508/11792.0218.DVUS01.

Respectfully submitted,



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Date: December 13, 2005

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